IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Garst
Serial No.: 09/903,954
Conf. No.: 3028
Filed: July 12, 2001
For: COMBINATIONS OF PROSTAGLANDINS AND BRIMONIDINE OR DERIVATIVES
Group Art Unit: 1614
Examiner: Fay, Z.

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Appeal Brief
Commissioner for Patents
Alexandria, VA 22313-1450

REPLY BRIEF

Appellants are in receipt of the Examiner's Answer mailed September 3, 2008, and after carefully reviewing this correspondence they have filed this Reply Brief in response thereto.

REMARKS

Claims 21-25 and 27 have been rejected as allegedly *prima facie* obvious over Yavitz, E., OCULAR SURG. NEWS 17:28 (September 1999) and Woodward (US Patent 5,877,211). Appellants filed an Appeal Brief on January 25, 2007 and separately argued the patentability of each of the pending claims.

The Examiner's Answer contained a restatement of the Grounds of Rejection, which has already been addressed in the Appeal Brief. The Examiner's Answer also contained a Response to Argument section. However, this section of the Examiner's Answer does not actually respond to the Appellant's arguments or apply the law correctly for at least two reasons.

The Examiner's Answer relies upon *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007) (hereafter "KSR") for the proposition that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." The Examiner then attempts to frame the principal issue as "whether the combination of an alpha adrenergic agent, such as brimonidine and a prostaglandin receptor agonist would have been obvious at the time of invention, given the scope and content of the prior art, the level of ordinary skill in the art and the difference between the claimed invention and the prior art". Examiner's Answer at page 5.

However, appealed claims 21-25 and 27 are all directed to methods "of treating degeneration of the optic nerve of a mammal in need of such treatment", rather than to the combination of an alpha adrenergic agent and a prostaglandin receptor agonist. Of course, even assuming *arguendo* that this "combination" is known, 35 U.S.C. §101 provides that new and useful processes are patentable; such "processes" include "a new use of a known process,

machine, manufacture, composition of matter, or material." 35 U.S.C. §100. Therefore, the Examiner's arguments drawn to the patentability of a "combination" or material are not, without more, germane to the patentability of a new use of that combination.

The Examiner's Answer concludes "it is the examiner's position that it would have been obvious to combine a prostaglandin receptor agonist and an alpha adrenergic receptor agonist and use the combination for protection of ophthalmic nerve, given the recognition by the prior art, that brimonidine, an alpha adrenergic agonistic nerve has been used as a neuroprotective agent and the recognition that glaucoma causes damage to optic nerve and the claimed prostaglandins have been used for the treatment of glaucoma." Examiner's Answer pages 5 and 6 (emphasis added).

Whether or not combining a prostaglandin and an alpha receptor agonist is obvious is respectfully not the issue. The question is whether a method of treating degeneration of the optic nerve is made obvious to a person of ordinary skill in the art by the disclosures of Yavitz and Woodward. Applicants respectfully contend that the present invention is not obvious for the reasons of record in the Appeal Brief (particularly but not exclusively on pages 9-11), which are hereby incorporated by reference as part of this Reply Brief, and for the additional reasons presented below.

Yavitz states that, in a very preliminary study, "raising the pressure in the eye to 80 mm Hg or above, which all microkeratomes must do in order to make a [corneal] flap, causes nerve loss in the nerve fiber layer due to either hypoxia [oxygen starvation] or apoptosis", in each case due to a mechanical crush injury to the intraocular nerve fiber layer caused by the elevated intraocular pressure (IOP), transiently required during LASIK. See *Yavitz* at 28, col. 1, ¶ 3.

To counteract this nerve loss each test subject used brimonidine, a known ocular hypertensive, for one week before the operation and for 4 weeks after the operation. See *Yavitz* at 28, col. 1, ¶ 4. In this way the intraocular pressure is reduced during the treatment period, thus also reducing the possible damage initially caused by a mechanical crush injury and reducing the possibility post operation than any such damage suffered during the LASIK surgery will be exacerbated due to heightened IOP.

Importantly, Yavitz does not in any way indicate that brimonidine's effect in these experiments proceeds in any way other than by decreasing IOP. Thus, a person of ordinary skill in the art would not understand Yavitz to have indicated that brimonidine is capable of treating degeneration of the optic nerve, but rather would understand that prevention of mechanical crush injury can be caused by eliminating high IOP through the use of the ocular hypotensive, brimonidine. Although Yavitz uses the word "neuroprotective" to describe the possible effects of brimonidine in this study, neuroprotective drugs are generally defined as agents that work, by a variety of mechanisms, "to minimize the damage that occurs when neurons are deprived of oxygen and nutrients". *See, e.g.*, *Neuroprotective Drugs in* ISCHEMIC STROKE AND TIA TREATMENT OPTIONS AT THE MAYO CLINIC, www.mayoclinic.org/stroke/ischemic-stroke.html (accessed October 31, 2008). By this generally used definition, Yavitz does not provide any reason for a person of ordinary skill in the art to believe that brimonidine is neuroprotective, as such a person would regard that the studies described in Yavitz use brimonidine preoperatively , a prophylactic to prevent neural damage caused by hypoxia due to high intraocular pressure and postoperatively to maintain low intraocular pressure, rather than as a treatment to minimize damage occurring when neurons are already deprived of oxygen and nutrients.

Since the Appeal Brief was filed in this matter, the United States Court of Appeal for the Federal Circuit has issued two opinions clarifying the United States Supreme Court's KSR opinion. In the first of these, *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.,*

520 F.3d 1358, __ U.S.P.Q.2d ___ (Fed. Cir. 2008)(slip op. 2007-1223) the Federal Circuit court held that, while KSR eschews a rigid TSM (teaching, suggestion, motivation) test, " a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis". The TSM test, "flexibly applied, merely assures that the obviousness test proceeds on the basis of evidence . . . that arises before the time of invention as the statute requires." *Id.* slip op. 2007-1223 at 11 and 12. In this case the court found that the invention was not obvious since there was no showing that one of ordinary skill in the art would follow the exact route that produced a claimed composition, the anticonvulsant drug topiramate, since topiramate was originally discovered as an intermediate in the course of developing and anti-diabetic type drugs—an ordinary artisan in that field would have had to (at the time of invention without any clue of later claimed potential utility of topiramate) had some reason to stop at and test it for properties far afield from the purpose surrounding its original development in the first place.

The second opinion, also a chemical case, was *Eisai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd.,* ___ F.3d __, __ U.S.P.Q.2d ___ (Fed. Cir. July 21, 2008) (slip op. 2007-1397, 1398). In this case the patent at issue was directed to the proton pump inhibitor rabeprazole and its salts. Rabeprazole is related to other prior art proton pump inhibitors such as lansoprazole and omeprazole, differing solely by the nature of the group at the 4 position of the pyridine ring. In upholding the patentability of the claims to rabeprazole, the Federal Circuit found that KSR presumes that the record before the time of invention would support some reasons for narrowing the prior art universe to a 'finite number if identified, predictable solutions'. However "[t]o the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these 'identified, predictable solutions' may present a difficulty hurdle because potential solutions are less likely to be genuinely predictable." *Id.* slip op. 2007-1397,1398 at 8).

In the present case, it is known from Yavitz that the claimed alpha adrenergic agonists are ocular hypotensive agents, and that they may be prophylactic in the prevention of damage due to

elevated IOP caused by use of a microkerotome. On the basis of Woodward, "[g]laucoma is a disease of the eye characterized by increased intraocular pressure", Woodward, column 1, lines 16-17, and that "one of the sequelae of glaucoma is damage to the optic nerve head caused by 'cupping'", presumably due to the high IOP. Again, Woodward defines neuroprotection by saying "there is an unmet need for agents that have neuroprotective effects in the eye that can stop or retard the progressive damage that occurs . . . as a result of glaucoma [i.e., caused by elevated IOP]", and states that "some prostaglandins are highly effective ocular hypotensive [i.e. IOP-lowering] agents and are ideally suited for the long-term medical management of glaucoma."

Thus, the definition of neuroprotection used in Woodward is also inconsistent with the general definition known to those of ordinary skill in the art and given above, defining neuroprotective agents as agents having activity "to minimize the damage that occurs when neurons are deprived of oxygen and nutrients".

Finally, there is no teaching or suggestion, as required under the *Ortho* and *Esai* line of obviousness decisions, in the combination of Yavitz and Woodward that would motivate a person of ordinary skill in the art to combine an alpha adrenergic agonist and a prostaglandin in the treatment (as distinct from the prevention) of degeneration of the optic nerve. Although Woodward discusses the use of EP2 agonists to treat ocular nerve damage, not all such agonist compounds are themselves prostaglandins. Yavitz does not discuss agents other than brimonidine and Woodward does not discuss alpha adrenergic agonists.

For these reasons, Appellants respectfully maintain that the invention of appealed claims 21-25 and 27 is patentable, and respectfully requests that the Board reverse the Examiner's rejection of these claims.

No fee is thought is due in connection with this communication. However, if Appellants are in error in this regard, please use Deposit Account No. 50-4004 for the payment of any fee (including any extension fee) now due.

Respectfully submitted,

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